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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,424	06/30/2003	Louis D. Falo JR.	076333-0325	8081

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,424	FALO ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *13-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0.

DETAILED ACTION

1. Applicant's election of Group I, Claims 1-12, without traverse, in the paper filed 3/17/05, is acknowledged.

2. Claims 13-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-12 are being acted upon.

3. The declaration is objected to because of uninitialed changes in the post office address of Inventor Falo. A new declaration is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, and 4-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for, a formulation comprising a hybridoma, said hybridoma comprising a DC and a tumor cell,

does not reasonably provide enablement for, a formulation comprising a hybridoma, said hybridoma comprising a DC and a virally infected cell.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to

enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

A review of the specification reveals that the formulations of the instant claims are defined as "prophylactic and therapeutic agents against tumor and viral infection" (page 1), "can induce CD8+ CTL" (page 3), and "protect against viral infection" (page 4). Clearly then, the formulations of the instant claims are pharmaceutical compositions and require enablement as such. The specification provides no teachings sufficient to enable claims drawn to a DC hybridoma which induces effective anti-virally-infected cell immunity. Note that the specification discloses background references and examples that deal *exclusively* with anti-tumor DC responses and anti-tumor DC hybridomas. Anti-virally-infected cell immunity is disclosed only in concept, a concept that was not enabled in 1997.

In the case of HIV infection the situation is even more unpredictable given the fact that both DCs and T cells are infected by the virus. As taught by Frank et al. (2002):

"A dendritic cell (DC) encountering an immunodeficiency virus should pose a threat to the virus, by efficiently processing and presenting viral antigenic determinants to activate specific anti-viral T and B cell immunity. While this may occur *in vivo*, it is apparent that DC-entrapped viruses can freely spread between cells, move to distal tissues, and proliferate rapidly particularly upon meeting CD4+ T cells. In fact, the latter is further augmented when the T cells are activated. Thus, it seems that immunodeficiency viruses exploit

the unique ability of DCs to survey the periphery and capture incoming pathogens, traffic around the body often targeting the lymphoid tissues, and efficiently communicate with naive and memory T cells. Combined with the fact that DCs are likely the first leukocytes interacting with virions crossing the mucosae, these features provide the basis on which the virus maximizes its chance to establish infection even in the face of immune activation."

Given this teaching, it would seem then that the formulations of the instant claims would be more likely to exacerbate viral infections than to treat or prevent them. The reference further teaches that other viruses, including herpes simplex virus, measles virus, sendai virus, vaccinia virus, and cytomegalovirus infect DCS and down-modulate their antigen presenting functions. Accordingly, the use of the DC hybridomas of the instant claims to induce effective anti-virally-infected cell immunity would be highly unpredictable. Said unpredictability would then require undue experimentation in using the formulations of the instant claims *in vivo* as disclosed in the specification.

See also Roberts (2004, IDS); in a publication entitled, *Are HIV Vaccines Fighting Fire with Gasoline?*, the author teaches that activating T cells in an attempt to fight HIV may actually exacerbate disease. The reference notes that HIV preferentially infects, and grows better in, activated T cells (a concept known as of the priority date of the instant application). Clearly then, given the very basic questions still to be answered as recently as 2004, the formulations of the instant claims were at best highly unpredictable and requiring of undue experimentation as of the 1997 priority date.

Also note that the claims are drawn to at least one "hybridoma". As taught by Stites et al. (1987), a hybridoma comprises, "a transformed cell line grown *in vitro* that is a somatic hybrid of 2 parent cell lines". Note particularly the term "transformed". As taught be Lewin (1987) "transformed" is defined as "a state of unrestrained growth in culture, resembling or identical with the tumorigenic condition". As can be seen in Janeway et al. (1994) it is the immortal tumor cell that contributes the ability to grow indefinitely to a hybridoma. Returning to the instant invention comprising a mortal DC and a mortal virally-infected cell, it is clear that neither the mortal DC nor the mortal virally-infected cell is capable of contributing transformation/immortality to the

claimed formulation, thus, in addition to failing to teach how to use the claimed formulation for its intended use (as set forth above), the specification also fails to teach how to make the "hybridoma" of the instant claims. Given the failure of the specification to teach how to make and how to use the formulation of the instant claims, said formulation is considered to be highly unpredictable and requiring of undue experimentation.

A review of the specification shows that no examples of hybridomas comprising a DC and a virally-infected cell are disclosed, i.e., no such formulations are made and none are shown to have any biological or pharmacological activity.

Accordingly, as set forth above, it is the Examiner's position that the specification fails to enable one of skill in the art to make or use the DC/virally infected cell formulations of the instant claims.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Peters (1981).

Peters teaches a formulation comprising a hybridoma having a first DC (from spleen) fused to a sarcoma cell (see entire document) capable of inducing effective CTL immunity.

The reference clearly anticipates the claimed invention.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992).

Guo et al. teaches a plurality of hybrids (or hybridomas) comprising an antigen-presenting B cell and a carcinoma cell, in a ration of 1:10 (see particularly page 520, columns 2-3, 11.). The reference teaches that the hybrids comprise cells that express both tumor-specific antigens and the machinery for antigen presentation (see particularly page 518, column 1), that said hybrids are immunogenic, and that said hybrids induce a protective anti-tumor immune response that might otherwise "escape immune surveillance because they do not express signals that are essential for activation of the host immune system" (see particularly page 520, column 1 and page 518, column 1) upon administration to a subject.

The reference teaching differs from the claimed invention only in that it does not teach the use of a DC as the antigen presenting component of the hybrid.

Sornasse et al. teaches that , while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo* (see particularly pages 16-17, Results). The reference teaches the superiority of DCs over B cells for *in vivo* use, "Our data emphasize the main role of DC in initiating primary responses *in vivo*" (see page 18, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a plurality of hybrids (or hybridomas) comprising an antigen-presenting B cell and a carcinoma cell, said hybrids comprising cells that express both tumor-specific antigens and the machinery for antigen presentation, as taught by Guo et al., substituting a DC for the B cell in said hybrid, as taught by Sornasse et al.. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution because, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo*, as taught by Sornasse et al. "Our data emphasize the main role of DC in initiating primary responses in vivo".

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992), as applied to Claims 1, 2, and 5-12 above, in further view of The Merck Manual (1992).

Guo et al. and Sornasse et al. have been discussed above.

The combined reference teachings differ from the claimed invention only in that they do not teach a formulation wherein the second cell is a tumor cell selected from the group consisting of melanoma cells, lung carcinoma cells, sarcomas, prostate carcinoma cells, breast carcinoma cells, colon carcinoma cells and cervical carcinoma cells.

The Merck Manual teaches that conventional treatments offer no proven benefit for melanoma (see particularly page 1287, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to provide the formulation for inducing effective CTL immunity of the combined Guo et al. and Sornasse et al. references, substituting a melanoma cell for the tumor cell in said formulation. One of ordinary skill in the art would have been motivated to provide said melanoma cell in the formulation and thus, produce a formulation for inducing effective CTL immunity against melanoma given the teachings of the Merck Manual that conventional treatments offer no proven benefit for melanoma.

11. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-12 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 of copending Application No. 11/089,025. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-3 and 5-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-3 and 5-12 of U.S. Application No. 09/208,549. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '549 application recite a formulation and pharmaceutical composition comprising a hybridoma having an antigen presenting cell fused to a tumor cell. The additional limitation of the hybridomas of the '549 patent, that they induce effective CTL-dependent immunity, does not render these product claims, reciting the same physical limitations, patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

16. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

6/1/05

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